Effect of vildagliptin and probiotic alone and in combination on cardio-metabolic dysfunction and glucagon like peptide-1 (GLP-1) gene expression in streptozotocin induced Diabetes in rats

Thesis

Submitted in partial fulfillment of the
requirement for the degree of
M.Sc. in Pharmacology

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2015

ABSTRACT

Type 2 diabetes mellitus (T2D) is a metabolic disorder that is characterized by high blood glucose due to insulin resistance and/ or relative insulin deficiency.

The aim of this work is to highlight the potential protective effect of vildagliptin, and probiotic on cardiac dysfunction in streptozotocin-induced diabetic rats.

Diabetes mellitus was induced in male albino rats by intraperitoneal injection of a single dose of streptozotocin (40 mg/kg). Rats were divided into five groups; one non diabetic control group, and four diabetic groups (diabetic, vildagliptin treated, probiotic treated, and combined vildagliptin + probiotic treated groups).

Vildagliptin (50 mg/kg), and probiotic (50 mg /kg) were administered orally daily for 6 weeks to study their effects on serum glucose, glycosylated hemoglobin, insulin, reduced glutathione, malondialdehyde levels. Glucagon like peptide-1 gene expression in cardiac tissue, cardiac contractility, electrocardiogram (heart rate, PR interval, QRS interval, QTc interval were estimated), and histopathological analysis of cardiac tissue were also performed.

The present study revealed that STZ induced diabetes led to significant increase in serum glucose level, and HbA1c by 156%, 154% respectively. STZ caused significant decrease in serum insulin level by 75%. MDA increased significantly in STZ induced diabetic rats by 830%, and GSH decreased significantly by 63%.

The present work also proved that vildagliptin treatment significantly decreased the level of serum glucose in STZ-induced diabetic rats by 32%. At the same time probiotic treatment significantly decreased the serum glucose level by 29%, and combined vildagliptin and probiotic treatment significantly decreased it by 35%. Vildagliptin

treatment and probiotic treatment significantly decreased HbA1c similarly by 29%, while combined treatment significantly decreased it by 44%. Vildagliptin significantly increased the serum insulin in STZ-induced diabetic rats by 127%, while probiotic significantly increased it by 140%, and combined treatment significantly increased serum insulin level by 162 %.

Vildagliptin treatment reduced MDA in STZ-induced diabetic rats by 46%, and increased GSH by 64%, while probiotic reduced MDA by 44.5%, and increased GSH by 63%, and combined treatment reduced MDA by 64%, and increased GSH by 95%.

STZ-induced diabetes led to a decrease in GLP-1 gene expression in cardiac tissue by 87.7%. Vildagliptin treatment increased the gene expression by 258.5%, probiotic treatment increased it by 295%, while combined treatment increased it by 432.5%.

Cardiac contractility was decreased in STZ diabetic rats by 21%. It was increased with vildagliptin treatment by 62%, with probiotic by 84%, and with vildagliptin+ probiotic by 88%. These results indicate improvement in GLP-1 gene expression and cardiac contractility with probiotic than with vildagliptin, and with combined treatment than with either drug alone. ECG data showed that vildagliptin caused significant decrease in heart rate, and prolonged QTc interval.

Histopathological examination by light microscopy using hematoxylin and eosin revealed granulation tissue, congestion, necrosis, vacuolative degeneration in diabetic groups. Sections stained by Masson's Trichrome showed interstitial fibrosis in diabetic group which was less with treatment by vildagliptin, and probiotic.

Key Words: Diabetes mellitus, GLP-1 gene expression, oxidative stress, cardiac contractility, vildagliptin, probiotic.